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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,570	06/02/2006	Hans H. Liao	8127-66576-05	3622

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EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
07/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,570	LIAO ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10,13-33,35-41,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-10, 13-33, 35-41, 66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims:

Claims 1-65 were pending. By this amendment, claims 4, 11, 12, 34 and 42-65 are cancelled. Claim 67 is new. Therefore, claims 1-3, 5-10, 13-33, 35-41 and 66-67 are present for examination.

Objections and rejections not reiterated from the previous Office Action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-10, 13-33, 35-41, 66 and 67 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the pages 19 and 25 of the specification teaches examples of cells such as mammalian cells (human, murine and bovine), plant cells, fungal cells etc. Furthermore applicants argue that the specification on page 21 teaches numerous specific examples of enzymes that can be used to produce 3-HP in a cell. Moreover, Applicants argue that additional examples of particular enzyme sequences that can be used in the claimed cells can be identified by searching publicly available databases (such as the NCBI website) for these enzymes. Therefore, there is adequate written description for the enzymes listed in the claims.

Applicant's argument has been carefully considered but not found persuasive.

While applicants recite that any type of cell including mammalian, plant, yeast etc. can be transformed with any beta-alanine/pyruvate aminotransferase having at least 90% sequence identity to SEQ ID NO: 20 and the specification on page 29 states that any nucleic acid or peptide having the desired enzymatic activity can be identified and obtained using common molecular cloning techniques (including PCR, sequence alignment tools, hybridization, and the like), Applicants have not shown any other type of cell transformed with any other beta-alanine aminotransferase comprising up to 10% variation relative to the specific sequence of SEQ ID NO: 20 wherein said sequence is transformed into any cell type.

Using the above common molecular cloning techniques (including PCR, sequence alignment tools, hybridization, and the like), Applicants used an available beta-alanine/pyruvate aminotransferase from *P. putida* to identify the beta-alanine/pyruvate aminotransferase of *P. aeruginosa* PAO1, a closely related microorganism. The alanine/pyruvate aminotransferase of SEQ ID NO: 20 was cloned in an expression plasmid and transformed in an *E. coli* strain.

However as of the filing date of the instant application, sequence alignments from the various databases do not show any sequence identical to SEQ ID NO: 20/19 or sequences with at least 90% sequence identity to SEQ ID NO: 20/19 (see SCORE results). Furthermore the specification does not teach transforming any other type of cell including any plant or animal cell to produce 3-HP. Applicants specification speculates that one skilled in the art will understand that similar methods can be used to clone a beta-alanine/pyruvate aminotransferase from other

organisms, such as *Streptomyces coelicolor* A3, *Corynebacterium glutamicum* ATCC 13032, and rat.

However the specification does not describe how to predict the structure of the genus of sequence with 90% identity to SEQ ID NO: 20 based on the structure of SEQ ID NO: 20. This is because the specification does not teach a structure/function correlation for any alanine/pyruvate aminotransferases including the alanine/pyruvate aminotransferase of SEQ ID NO: 20/19 (The active site or consensus sequence essential for function, binding site etc. were not disclosed).

Furthermore Applicants argue:

It is also asserted that the specification does not provide examples of enzyme sequences having variant sequences that retain enzyme activity. Applicants disagree. The specification provides several examples of each enzyme, and those examples have varying degrees of sequence identity, as shown below: beta-alanine/pyruvate aminotransferase protein sequences: SEQ ID NO: 18 and 20 have 76.6% sequence identity (see Exhibit A);3-hydroxypropionate dehydrogenase sequences: SEQ ID NO: 28 (Genbank Accession No: AAG06957) and Genbank Accession No: AAA25891 have 14% sequence identity (see Exhibit B); alanine 2,3-aminomutase sequences SEQ ID NOS: 22 and 24 and 26 have 59 % to 100 % sequence identity (see Exhibit C). In addition, one skilled in the art based on the teachings of the application and the knowledge in the art would be able to generate a sequence having at least 90% sequence identity to a given sequence, and test whether that sequence has the desired enzyme activity.

However, various proteins that may have common sequences may not be functional equivalents (see for example introduction in Haft et al., Nucleic acid research, 2001, vol. 29, No. 1, pages 41-43). Haft et al teach that while similar function is implied between sequences of highest similarity of different species: conserved function is not a formal criterion used to build clusters of orthologous groups. Therefore a sequence comprising 90% may encode an enzyme with a different function. The specification does not describe the relevant common identifying characteristics for all alanine/pyruvate aminotransferases.

Applicants further argue that:

"It is asserted on page 5 of the Office action that specification indicates that it is advantageous to delete the lactate dehydrogenase gene in the claimed cells. Applicants agree that it can be advantageous to functionally delete the lactate dehydrogenase in the claimed cells, as it (as well as other enzymes) competes with the beta-alanine/pyruvate aminotransferase for pyruvate, thus decreasing detectable 3-HP production. However, it is not Applicants' position (nor stated as such in the specification) that the lactate dehydrogenase must be deleted in order to produce the desired product. Instead, it is merely an exemplary embodiment that permits enhanced production of 3-HP or other downstream product".

In paragraph [0148] of the specification, applicants assert that deletion of lactate dehydrogenase, the enzyme that catalyzes the formation/interconversion of lactic acid and pyruvate in *E. coli,* results in elimination of lactic acid formation, hence is advantageous for the detection of the formation of 3-HP because of the similarity in structure and chromatographic behavior of lactic acid and 3-HP. Thus the specific *E. coli* deletion mutant is useful not only to increase availability of substrate but also to distinguish 3-HP that is produced since the chromatographic behavior between lactic acid and 3-HP is not distinguishable. Thus strains without deletion of lactate dehydrogenase are indistinguishable from strains that only produce lactic acid.

As stated in the previous office action, one skilled in the art would not recognize that the Applicant was in possession of the claimed invention as a whole at the time of filing. This is because Applicants have neither provided an actual reduction to practice, nor provided sufficient relevant identifying characteristics for all alanine/pyruvate aminotransferases with a complete or partial structure. Applicants have not shown any physical and/or chemical properties common to all alanine/pyruvate aminotransferases or functional characteristics coupled with a known or disclosed correlation between structure and function. Furthermore Applicants have not provided a method of making any host cell (i.e. any plant or animal, yeast cell etc.) transformed with any

alanine/pyruvate aminotransferases comprising at least 90% identity to SEQ ID NO: 20/19 with the capacity to produces 3-HP. Based on the sequence alignment results and the single strain of recombinant prokaryotic cell (BW25113 .DELTA.ldhA::cam) that produces 3-HP (transformed with the specific sequence of SEQ ID NO: 20), one of skill in the art cannot predict a cell from any source (eukaryotic or prokaryotic).

Therefore claims 1-3, 5-10, 13-33, 35-41, 66, 67 remain rejected as under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 1-3, 5-10, 13-33, 35-41, 66, 67 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *E. coli* strain (BW25113 .DELTA.ldhA::cam cells that lack the Lactate dehydrogenase gene with a vector transformed with the *Pseudomonas aeruginosa* alanine/pyruvate aminotransferase (SEQ ID NO: 19) and the 3-hydroxypropionate dehydrogenase (mmsB gene) of SEQ ID NO: 27 to produce 3-HP or while it is enabling for *E. coli* cells (BW25113 .DELTA.ldhA::cam cells that lack the Lactate dehydrogenase gene) transformed with a vector comprising the *Pseudomonas aeruginosa* alanine/pyruvate aminotransferase (SEQ ID NO: 19), the 3-hydroxypropionate dehydrogenase (mmsB gene SEQ ID NO: 27) and a mutant *Bacillus subtilis* lysine 2,3-aminomutase (SEQ ID NO: 21) to produce 3-HP, does not reasonably provide enablement for any other cell type from any source.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims are not commensurate with the enablement provided by the disclosure with regards to the extremely large number of cell types and nucleic acids that encode the various enzymes broadly encompassed in the claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988).The factors include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

Applicants argue that two different beta.alanine/pyruvate aminotransferases having only 76.6% sequence identity can be used to produce 3,HP in the cells of a non-native organism, thus one skilled in the art can use variants with 90% sequence identity to produce 3-HP.

Applicant's argument has been carefully considered however not found persuasive.

As stated above, various proteins that may have common sequences may not be functional equivalents (see for example introduction in Haft et al., Nucleic acid research, 2001, vol. 29, No. 1, pages 41-43). Haft et al teach that while similar function is implied between sequences of highest similarity of different species: conserved function is not a formal criterion used to build clusters of orthologous groups. Therefore a sequence comprising 90% does not necessarily encode a protein with the same function. The specification does not describe the relevant identifying characteristics for all alanine/pyruvate aminotransferases with up to 10% variation in sequence.

Furthermore applicants argue that it is not applicant's position that the lactate dehydrogenase must be deleted in order to produce the desired product. Instead, it is merely an exemplary embodiment that permits enhanced production of 3-HP or other derivatives.

However as stated above, the specific *E. coli* deletion mutant is useful not only to increase availability of substrate but also to distinguish between lactic acid and 3-HP because the chromatographic behavior of lactic acid is not distinguishable from that of 3-HP. Thus a host cell, including mammalian, plant, yeast etc that does not comprise a deletion of lactate dehydrogenase may produce lactic acid that is indistinguishable from 3-HP in the presence or absence of a functional alanine/pyruvate aminotransferases with at least 90% identity to SEQ ID NO: 19.

Furthermore applicants argue:

"The specification is sufficiently enabled for cells of any type to produce 3-HP using the enzyme sequences provided in the application, as well as those sequences known in the art at the time of the invention, or identified after the invention. As discussed above, the specification provides several examples of particular sequences for each enzyme. In addition, other examples were available as of the priority date of the application. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public".

However while Applicants recite that any type of cell including mammalian, plant, yeast etc. can be transformed with any beta-alanine/pyruvate aminotransferase comprising at least 90% sequence identity to SEQ ID NO: 20 and that the specification on page 29 states, any nucleic acid or peptide having the desired enzymatic activity can be identified and obtained using common molecular cloning techniques (including PCR, sequence alignment tools, hybridization, and the like), Applicants have not shown any other type of cell transformed with any other beta-alanine aminotransferase comprising up to 10% variation relative to the specific sequence of SEQ ID NO: 20.

Applicants used the known available beta-alanine/pyruvate aminotransferase of *P. putida* to identify the beta-alanine/pyruvate aminotransferase of a closely related microorganism, namely *P. aeruginosa* PAO1 comprising SEQ ID NO: 20 encoding SEQ ID NO: 19. The alanine/pyruvate aminotransferase of SEQ ID NO: 20 was cloned in an expression plasmid and transformed in a specific *E. coli* strain. However as of the filing date of the instant application, sequence alignments in the various databases do not show a significant number of sequences with at least 90% sequence identity to other beta-alanine/pyruvate aminotransferase of SEQ ID NO: 20/19 (see SCORE results). Furthermore the specification does not teach transforming any other type of cell including any plant or animal cell to produce 3-HP. Applicants specification speculates that one skilled in the art will understand that similar methods can be used to clone a beta-alanine/pyruvate aminotransferase from other prokaryotic microorganisms, such as *Streptomyces coelicolor* A3, *Corynebacterium glutamicum* ATCC 13032, and cells derived from a mammalian organism such as rat. However the specification does not describe a structure/function correlation for any sequence with 90% identity to SEQ ID NO: 20 where the skilled artisan can predict the structure of the genus of functional variants broadly encompassed. As stated above, various proteins that may have common sequences may not be functional equivalents (see for example introduction in Haft et al., Nucleic acid research, 2001, vol. 29, No. 1, pages 41-43). Haft et al teach that while similar function is implied between sequences of highest similarity of different species: conserved function is not a formal criterion used to build clusters of orthologous groups. Therefore a sequence comprising 90% does not necessarily encode a protein with the same function. With this premises the product produced in a

transformed cell from any source (mammalian, plant, yeast etc) is unpredictable because one of skill cannot decipher between lactic acid and 3-HP produced in host cells.

Furthermore the prior art does not teach use of any other cell comprising animal, plant or microbial cell as a platform for the production of 3-HP. Thus using any cell comprising a functional lactate dehydrogenase in concert with sequences with up to 10% variation wherein said modification is not taught in the specification would be unpredictable.

Furthermore the specification does disclose all possible interfering metabolic pathways, and how these pathways can be manipulated in all possible cells including in any animal, plant or microbial cells, suitable promoters to use, codon optimization for specific cell types. Thus the skilled artisan would require performing undue amount of experimentation to decipher all the above parameters in view of producing a cell that produces a 3-HP or derivatives. Therefore the rejection of claims 1-3, 5-10, 13-33, 35-41, 66, 67 is maintained.

Conclusion: No claims are allowed.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANDREW WANG can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus/
Examiner, Art Unit 1656,
6/29/2009.

/Andrew Wang/
Supervisory Patent Examiner, Art Unit 1656